COVID-19

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acute respiratory distress syndrome, which itself can damage the kidney, Ronco noted. High airway pressure from mechanical ventilation these patients receive to help them breath may also inadvertently cause harm. The infection can set off a cytokine storm, a severe immune reaction in which the immune system floods the body with inflammatory chemicals that can also directly damage the kidney, he said.

"This is clearly a multifactorial situation," Ronco said. "In these patients, there are several mechanisms that may induce damage to the kidney. Some of them are direct and some of them are indirect."

Complicating matters, patients with COVID-19 often show up at the hospital dehydrated as a result of not feeling well, diarrhea, and not eating or drinking as much as they usually do, Durvasula said. And patients who need mechanical ventilation may be given diuretics to get rid of excess fluid in order to improve their oxygenation, which may inadvertently cause low fluid levels in the body, which, in turn, can contribute to tubular injuries or dysfunction, he said.

There is also emerging evidence that COVID-19 patients may be prone to developing blood clots. For example, Durvasula said he and his colleagues have seen COVID-19 patients receiving dialysis develop clots that block off their dialysis circuits requiring treatment with anticlotting drugs.

"We are hearing reports that patients may similarly be developing spontaneous clots in large veins in their bodies," he said. "This begs the question whether they may be forming clots in the small vessels of the kidney and that could be a mechanism of kidney injury."

Ronco noted that the flood of inflammatory molecules caused by a cytokine storm can cause dysfunction in the lining of the blood vessels throughout the body and in the muscle tissue of the heart, and it can contribute to excessive clot formation. The kidney may also be directly damaged as it filters out harmful molecules (damage-associated molecular patterns) released by cells killed by the infection or inflammation. The immune system's attempts to correct the excessive inflammation can also cause harm, he noted.

Currently, physicians are still relying primarily on supportive intensive care to help severely ill COVID-19 patients recover, Durvasula said. This includes trying to maintain an optimal amount of fluid in the body—not too much or too little. Ronco noted that maintaining optimal blood pressure and treating patients who develop clots with anticoagulant drugs can also help in the recovery of COVID-19 patients. Some anti-inflammatory drugs are also being used. Ronco and his colleagues are trying extracorporeal therapies that pump the blood out of the body to screen out some of the inflammatory molecules to help modulate the patient's immune response (3). Although he cautioned there are not yet data from randomized clinical trials to prove this is effective, "we only have expert opinion and experience."

"It is an option for patients to gain time and have their immune system respond and possibly get better," he said.

Several studies are underway of antiviral drugs to treat patients with COVID-19. The US Food and Drug Administration recently granted an emergency use authorization for the investigational antiviral drug remdesivir for severely ill COVID-19 patients (4). Preliminary results showed an 11-day average recovery time in patients taking the drug compared with a 15-day recovery time for those not taking the drug (5).

Direct assault?

There is also emerging evidence that the virus itself may directly infect the kidney. Using histological techniques and electron microscopy, researchers from Wuhan, China, examined kidney samples from 26 patients who died of COVID-19 and showed the SARS-CoV-2 virus was present in the kidneys (6).

"It's excellent work under some challenging circumstances," said Evan Farkash, MD, PhD, who recently published results of an autopsy of a single patient from Michigan who died as a result of COVID-19 complications that confirms the presence of the virus in the kidney in renal tubular cells using similar techniques (7). Using light microscopy, he found that tubular cells infected with SARS-CoV-2 were filled with vacuoles. Farkash noted that a previous coronavirus that caused a global outbreak of severe acute respiratory syndrome in 2003 reproduces in vacuoles. This could be evidence that SARS-CoV-2 is replicating in the kidney cells, but more studies are needed to confirm this, he said.

Since then, Farkash and his colleagues have examined kidney tissue from more patients who died from COVID-19 and found that the virus is often present and can also be found in the glomerulus.

The angiotensin-converting enzyme 2 (ACE-2) receptor that allows the virus to infect lung cells also infects kidney cells. "Mechanistically, it makes sense that the kidney could be infected," Farkash said. "The ACE-2 receptor is expressed at very high levels in the renal tubular epithelium. It is also expressed in endothelial cells as well as the podocytes in the glomerulus."

But more study is needed to determine how big of a role it plays, Farkash said. He noted that in the patient whose autopsy results were published, the virus was only present in a small part of the kidney, suggesting that other mechanisms may have played a larger role in the patient's kidney injury.

"The direct infection could have been an incidental finding, or it may have mattered very little or not at all," he said. He noted the virus was more widespread in the kidneys of other deceased patients. But it may just be a manifestation of the widespread disease in the patients' bodies, he said.

Durvasula called the autopsy findings "compelling." He also noted there is evidence from China of blood or protein in the urine of patients with COVID-19.

"When we hear descriptions of protein and blood in the urine, that tells us there is actually an intrinsic injury within the kidneys," he said. Both Farkash and Durvasula noted that biopsy studies from living patients with COVID-19–related kidney injuries might provide more definitive evidence of the virus' role in kidney injury. But such biopsies are not likely to be collected unless it may help guide patient care, Durvasula said.

Although there has been a recent explosion in the numbers of studies about the effect of COVID-19 on the kidney, there are still many questions that need to be answered. For example, Durvasula noted that the number of COVID-19 patients requiring dialysis in the intensive care unit has varied in different parts of the country, with 20% to 40% of patients needing such care in some parts of the country (8). But only about 5% of COVID-19 patients at the hospitals Durvasula works with have required renal replacement therapy.

"As much as we've learned, there's still a lot we don't know about the mechanisms of acute kidney injury in COVID-19 patients," Durvasula said. ■

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Kidney biopsies for research: safety and feasibility

Additional kidney cores for research purposes can be successfully and safely obtained from 90% of diabetic patients undergoing clinically indicated kidney biopsy, according to a research letter in *CJASN*.

The authors report an interim analysis from the multicenter Transforming Research in Diabetic Nephropathy (TRIDENT) study, a longitudinal cohort study using direct analysis of kidney tissue to identify biomarkers and new therapeutic targets for diabetic kidney disease. The analysis included data on 176 patients enrolled in TRIDENT. All had clinical indications for kidney biopsy and consented to undergo collection of an additional biopsy core for the study.

Biopsy was performed in 160 patients, and a research biopsy core was successfully obtained from 144 patients. The reasons for not obtaining an additional core were operator's decision or needing all tissue for clinical purposes in 10 cases and bleeding/hematoma in six cases. The mean number of biopsy passes was 3.6. The indications for biopsy were excessive proteinuria in 65% of cases and rapid loss of kidney function in 24%.

Diabetic glomerulosclerosis was present in 82% of eligible research cores. Eleven patients (7%) experienced a total of 19 complications. Hematomas >5 cm occurred in seven patients, gross hematuria in three patients, and unplanned blood transfusion in three patients. Six patients had a prolonged hospital stay or readmission, but none required surgery or radiologic intervention.

Diabetic kidney disease is usually a clinical diagnosis, based on blood and urine test results rather than direct analysis of kidney tissue. There are limited data on the feasibility and safety of obtaining kidney biopsy cores for research purposes, as planned by the TRIDENT study.

This interim analysis shows a high rate of successful research core recovery in diabetic patients undergoing clinically indicated kidney biopsy, with low rates of adverse events. "These data will help to potentiate the safety of obtaining kidney tissue for research, ultimately improving care for patients with DKD," the researchers write. They plan a full analysis of biopsy complications and risk factors once TRIDENT recruitment is completed [Hogan JJ, et al. The feasibility and safety of obtaining research kidney biopsy cores in patients with diabetes: An interim analysis of the TRIDENT study. *Clin J Am Soc Nephrol* doi: 10.2215/CJN.13061019]. ■